Remarks

Applicant notes that the filing date of the application is June 30, 2003 and not as stated in item 2 of the Office Action.

Claims 1-11, 20-27 and 47-48 as amended are submitted herewith for the Examiner's consideration in response to the Office Action dated March 18, 2009.

Support for claims 1, 20 and 24 as amended to specify that the peptide fragment is "about 10-100 amino acid residues in length" is found in claim 10 of the previous claim version, and in the specification, for example in paragraph [0024] of the published application US 2007/0203054).

Claim 4 as amended recites "SEQ ID NO:3, or an analog thereof" and the previously recited terms "active fragment", "isoform" and "derivative" have been deleted.

Support for claim 10 as amended to specify "25 to 75 amino acids" is found for example in paragraph [0024] of the published application.

Support for claim 20 as amended to specify that the claimed fusion protein further comprises "a molecule selected from an immunoglobulin (Ig) molecule or a fragment thereof, and a cytotoxic substance" is found for example in claim 22 as filed and in paragraphs [0058] and [0149] of the published application.

Claim 20 as amended further specifies that the claimed fusion protein is other than the fusion proteins of SEQ ID NOS:13-16. Applicant submits that the previous exclusion of SEQ ID NOS:17-18 from the scope of claim 20 was an inadvertent error.

Support for claim 47 as amended to specify "wherein the epitope is in the proximal domain of the NKp46 receptor" is found for example in paragraphs [0016] and [0026] of the published application.

Support for claim 48 as amended to specify "Threonine 225 replaced by an amino acid residue selected from the group consisting of Serine, Alanine and Asparagine" is found for example in paragraphs [0028] and [0069] of the published application.

The specification is amended in the Brief Description of the Drawing to reflect Figures 2, 3, 5, 8, 9 and 10, as requested by the Examiner.

No new matter has been added.

Rejections under 35 U.S.C. 102

Claims 1-3 and 24-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Mandelboim et al (WO 02/09298).

Mandelboim et al teaches a targeting complex, capable of targeting an active substance to a target cell, wherein the targeting complex comprises at least NKp46, NKp44, NKp30 or a functional fragment thereof. Mandelboim et al discloses the full-length proteins NKp46 (isoforms a and b), NKp44 and NKp30, as well as domains D1 and D2 of NKp46 and domains D1 and D2 of NKp44 (see for example Mandelboim et al, pages 3 and 61, and Sequence Listing). Mandelboim et al however, does not disclose a peptide fragment of an NCR of an NK cell comprising a linker peptide connecting the extracellular domain (ECD) of the receptor to the transmembrane portion (TM) of the receptor, wherein the peptide fragment is about 10-100 amino acid residues in length. Mandelboim et al in fact, does not disclose any NCR fragment that is about 10-100 amino acid residues in length.

In contrast, claims 1 and 24 as amended recite that the claimed peptide fragment is about 10-100 amino acid residues in length.

Accordingly, Mandelboim et al does not anticipate the presently claimed invention, and the rejection under 35 U.S.C. 102(b) should be withdrawn.

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Cantoni et al (Journal of Experimental Medicine, 1999, Vol. 189, No. 5, pp. 787-795).

Cantoni et al teaches molecular cloning, expression and biochemical characterization of NKp44. More specifically, Cantoni et al teaches a cDNA clone encoding an open reading frame of 276 amino acids and a putative ECD and TM thereof (see Cantoni et al page 790, 2nd column-page 791, 1st column). Cantoni et al however, does not disclose a peptide fragment comprising a linker peptide connecting the ECD to the TM, wherein the peptide fragment is about 10-100 amino acid residues in length.

In contrast, claim 1 as amended recites that the claimed peptide fragment is about 10-100 amino acid residues in length.

Accordingly, Cantoni et al does not anticipate the presently claimed invention, and the rejection under 35 U.S.C. 102(b) should be withdrawn.

Rejections under 35 U.S.C. 112

(a) Claims 1-11, 20-27 47-48 are rejected under 35 U.S.C. 112 first paragraph. The Office Action alleges *inter alia* that the specification fails to teach any isolated peptide fragment other than NKp46D2 that retains the ability to bind to viral infected cells or tumor cells, and that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventors had possession of the claimed invention at the time the application was filed.

Applicant respectfully refers to the teaching in the specification of NKp44LP (residues 136-190 of NKp44) and the fusion protein NKp44LP-Ig, the latter of which is shown to efficiently bind to viral infected cells (see for example paragraphs [0014], [0071], [0187] and [0188] of the published application). This teaching provides support for the claimed isolated peptide fragment.

Furthermore, Applicant respectfully submits that the teaching in the specification of NKp46D2 substitution mutants and the ability of fusion proteins comprising those mutants to bind to target cells provides sufficient support for a fragment such as SEQ ID NO:3 which retains the desired binding activity. More specifically, Example 5 of the specification teaches that Ig-fusion proteins of the mutants NKp46T125A and NKp46N216A show levels of binding to viral infected cells that are substantially identical to that exhibited by NKp46D2 (compare Fig. 6 and Fig. 3a), whereas the mutants NKp46T225A and NKp46T225N (i.e. threonine replaced by alanine and asparagine, respectively), show substantially reduced binding to the same cells. Example 6 teaches that the wild type residue threonine at position 225 or its replacement with asparagine is essential for binding to tumor cells, whereas mutations at positions 125 and 216 have no effect on tumor cell binding. Thus, the specification teaches that the amino acid residues at positions 125 and 216 are apparently non-essential for binding to viral infected cells and tumor cells, whereas residue 225 is essential for binding to viral infected cells and tumor cells. Accordingly, the specification provides support that SEQ ID NO:3, corresponding to amino acid

residues 215-254 of NKp46 i.e. including the essential amino acid residue at position 225 and even containing the non-essential residue at position 216, retains the desired binding activity.

Furthermore, claim 4 as amended recites "SEQ ID NO:3, or an analog thereof". The specification teaches that an analog may have an amino acid sequence different from that of the specific molecule, such as when at least one amino acid residue is substituted (see paragraph [0059] of the published application). Applicant respectfully submits that the aforementioned teachings of substitution mutants provide support for the recited embodiment of analogs, for example various conservative and non-conservative substitutions at positions 216 for binding to viral infected cells, and asparagine substitution at position 225 for binding to tumor cells.

Claim 20 as amended excludes SEQ ID NOS:13-16 as the claimed fusion protein. As aforementioned, the specification teaches the fusion protein NKp44LP-Ig (SEQ ID NO:18) which binds viral infected cells (see for example paragraph [0188 of the published specification). Accordingly, claim 20 as amended is supported by the teachings of the specification.

With respect to claims 24-27 directed to pharmaceutical compositions, Applicant respectfully submits that the specification provides an adequate teaching of how to make and use the composition, for example at paragraphs [0025]-[0030], [0069]-[0072], [0076]-[0081] and [0089]-[0094] of the published application.

Claim 47 is amended to recite "wherein the epitope is in the proximal domain of the NKp46 receptor". Applicant respectfully submits that the aforementioned teachings in the specification of NKp46D2 substitution mutants provides adequate support for claim 47 as amended. Applicant respectfully refers once again to the teachings in the specification of the various substitution mutations within D2 of NKp46 i.e at positions 125, 216 and 255 (see for example paragraphs [0069]-[0070] of the published specification). For example, mutation at position 216 by replacement of asparagine with alanine does not affect binding to viral infected cells or tumor cells (see paragraphs [0177] and [0183] of the published specification). Accordingly, the specification teaches point mutations in addition to those disclosed regarding position 225 and thereby provides support for the variant polypeptide of claim 47 as amended.

Applicant moreover respectfully points out that claim 47 recites that the amino acid substitution is "in an epitope required for recognition of viral infected or tumor cells", but the

claimed variant polypeptide is not limited to one which exhibits such binding activity. Indeed the specification teaches the utility of variants, such as threonine at position 225 replaced by alanine or asparagine, which have diminished binding to target cells (see for example paragraphs [0027]-[0028] of the published application).

With regard to claim 48, the specification discloses that substitution of threonine at position 225 with serine resulted in decreased binding to viral infected cells but similar binding to tumor cells (see paragraph [0069] of the published application). Accordingly, the teaching in the specification of point mutations at position 225 in which threonine is substituted with any of serine, asparagine or alanine, provides adequate support for claim 48 as amended.

Applicant further respectfully submits that in accordance with the foregoing comments and explanations regarding the teachings of the application, the specification reasonably conveys to one of skill in the art that the inventors had possession of the claimed invention at the time the application was filed.

(b) Claims 20-27 and 47-48 are rejected under 35 U.S.C. 112 second paragraph.

Claims 20 and 24 as amended recite "a linker peptide" thereby overcoming the lack of antecedent basis.

Claim 20 as amended indicates that the claimed fusion protein further comprises a molecule selected from an immunoglobulin (Ig) molecule or a fragment thereof, and a cytotoxic substance, and thus recites the identity of the other portion of the fusion protein.

Claim 20 as amended recites that the "fusion protein exhibits at least one activity selected from binding to a viral infected cell or binding to a tumor cell", thereby overcoming the alleged lack of clarity.

Claim 20 as amended recites "wherein said fusion protein is other than the fusion proteins of SEQ ID NOS:13-16", thereby overcoming the alleged lack of clarity.

Claim 1 as amended recites that the "peptide fragment exhibits at least one activity selected from binding to a viral infected cell or binding to a tumor cell", thereby overcoming the alleged lack of clarity.

Applicant respectfully submits that the aforementioned amendments in claims 1, 20, and 24 also serve to overcome the alleged lack of clarity in claims dependent thereon.

While the Office Action does not specify the reason for the rejection of claims 47-48 under 35 U.S.C. 112 second paragraph, Applicant respectfully submits that the amendment to claim 47 overcomes any alleged lack of clarity therein.

In accordance with the amendments and foregoing explanations, Applicant respectfully requests withdrawal of the rejections under 35 USC 112 first and second paragraphs.

Non-statutory Double Patenting

Claims 1-3, 47 and 24 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1, 5, 12 of copending application No. 10/580,428. Application No. 10/580,428 is abandoned, rending the rejection moot.

Claims 20-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1, 3, 4 of copending application No. 10/538,231. It is respectfully submitted that this issuance of this rejection is premature since the claims of application No. 10/538,231 are still pending, and that an appropriate Terminal Disclaimer will be filed upon allowance of that or the subject application, whichever occurs first.

Claim Objections

Claims 1 and 4 are objected to due to informalities as set out in item 4 of the Office Action. Claims 1 and 4 as amended incorporate the suggestions of the Examiner.

Respectfully submitted,

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